☐ 1: J Endocrinol Invest. 1995 Nov;18(10):806-8. Related Articles, Links

Undetectable luteinizing hormone levels using a monoclonal immunometric assay.

Barbe F, Legagneur H, Watrin V, Klein M, Badonnel Y.

Service de Biologie Medicale, Maternite Regionale, Nancy, France.

Previous studies have shown wide discrepancies among the results obtained with different immunometric assays. We present five cases (out of 4000 women) whose plasma luteinizing hormone was not detected using a LH immunometric assay (LH Stratus Baxter) but was recognized by other kits. These cases concerned one 28-year-old woman presenting with infertility and four postmenopausal women. The LH Amerlite kit gave detectable but low results. The results obtained with the other kits were > 7 IU/l. FSH levels were > 7 IU/l. In one case, sera were taken before and after the menopause; differences between the LH results increased. Discrepancies among LH assay kits have been attributed to variation both in standard curve calibration and in epitope specificity of the kit monoclonal antibodies. The Baxter kit might misrecognize some isoforms present in postmenopausal women. The present data illustrate the potential false results with such immunoassays in routine clinical laboratory testing. When undetectable LH results are not clinically explained or when disparities between LH and FSH are observed, we suggest using a second methodology or a bioassay if necessary. Improvement in LH assays and standardization might resolve the problem of discrepancies between the LH results.

PMID: 8787959 [PubMed - indexed for MEDLINE]

☐ 1: Endocrinol Metab Clin North Am. 1991 Mar;20(1):85-120. Related Articles, Links

Bioactivity of gonadotropins.

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Department of Pediatrics, University of Michigan Medical School, Ann Arbor.

It is now certain that both gonadotropins, LH and FSH, are synthesized, stored, and released within the circulation, and excreted as heterologous isoforms that can be distinguished by differences in their bioactive to immunoreactive potential and isoform distribution patterns. The bioactivity (which in this article has been defined as the ability of LH to induce T production in rat interstitial cells and FSH to induce E2 production (via aromatase) in rat Sertoli cells in vitro) results from the ability of gonadotropin isoforms to stimulate postreceptor binding functions upstream from G-protein activation and second messenger stimulation. Within the mix of the heterogeneous isoforms, there could be some that alternatively stimulate Gi protein and inhibit function or some that could stimulate G-protein activation for prolonged periods that extend beyond signal-receptor binding. Methods of separation of isoforms are not yet precise or sophisticated enough to distinguish these isoforms. Therefore, the measurement of in vitro bioactivity measures the sum of stimulatory and inhibitory influences on one defined end result. The immunologic potencies also measure the ability of certain selected antibodies to recognize epitopes on gonadotropin molecules, whether they are biologically active or, by virtue of CHO differences or changes in tertiary structure, biologically inactive. Nonetheless, in many instances, the results have been significantly different, with the bioactivity measurements showing greater excursions in stimulatory or inhibitory paradigms than the immunologic potencies. This has been especially true for FSH. Capitalizing on the usefulness of these methodologic advances, we have reviewed the contribution that measurements of gonadotropin bioactivity have made to our understanding of human puberty, which is a continuum in development from conception to adulthood.(ABSTRACT TRUNCATED AT 400 WORDS)

Publication Types:
- Review

PMID: 1903105 [PubMed - indexed for MEDLINE]

J Clin Endocrinol Metab. 1993 Aug;77(2):347-51. Related Articles, Links

Variants of human chorionic gonadotropin from pregnant women and tumor patients recognized by monoclonal antibodies.

Berger P, Schwarz S, Spottl G, Wick G, Mann K.

Institute for Biomedical Aging Research, Austrian Academy of Sciences, Innsbruck.

In biological fluids, hCG and its free alpha- (hCG alpha) and beta-subunits (hCG beta), occur in multiple forms. These various forms differ at the molecular level primarily in glycosylation, but also differ in protein backbone modifications corresponding to the urinary low molecular weight fragment of the hCG beta-subunit (beta-core fragment). This microheterogeneous nature can be demonstrated by isoelectric focusing in which variants are separated into bands with different isoelectric points (pI). To determine whether such isoelectric variants differ in antigenicity and consequently might escape immunoassay detection due to overspecificity of monoclonal antibodies (MCA), urinary pregnancy hCG (NIH, CR123) and tumor hCG preparations, such as a tumor-specific acidic variant of hCG (hCGav) and the hCG beta-core fragment, were separated by isoelectric focusing in the absence or presence of 8 M urea, or by sodium docedyl sulfate-polyacrylamide gel electrophoresis and enzymatically immunostained using an MCA panel directed against 17 different hCG epitopes. MCA against 14 different epitopes accessible on holo-hCG recognized all pI variants of pregnancy holo-hCG or tumor-derived hCGav, as was true for the three MCA recognizing epitopes hidden on holo-hCG but accessible on the free subunits after hCG dissociation by urea. We conclude that each individual pI-isoform of holo-hCG and its free subunits expresses the entire set of epitopes recognized by our MCA panel. The carbohydrate moieties that form a biochemical basis for hCG heterogeneity seem to be neither of major antigenic relevance, nor are they structurally related to any particular epitope. Thus, various glycosylation forms of hCG, hCG alpha, hCG beta, and hCG beta-core in normal as well as in pathological samples should safely be detectable and measureable by immunoassays employing MCA with appropriate subunit specificity.

PMID: 7688376 [PubMed - indexed for MEDLINE]

1: Endocrine. 1999 Apr;10(2):137-44. Related Articles, Links

Development and characterization of antibodies to a nicked and hyperglycosylated form of hCG from a choriocarcinoma patient: generation of antibodies that differentiate between pregnancy hCG and choriocarcinoma hCG.

Birken S, Krichevsky A, O'Connor J, Schlatterer J, Cole L, Kardana A, Canfield R.

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Human chorionic gonadotropin (hCG) exists in blood and urine as a variety of isoforms one of which contains peptide bond cleavages within its beta-subunit loop 2 and is referred to as nicked hCG (hCGn). This hCG isoform appears to be more prevalent in the urine of patients with certain malignancies and possibly in some disorders of pregnancy. Until now, only indirect immunoassays could be used to quantify hCGn. We report the development of two monoclonal antibodies (MAbs) to a form of hCGn isolated from a choriocarcinoma patient. This hCG isoform was not only 100% nicked, but also contained 100% tetrasaccharide-core O-linked carbohydrate moieties in its beta COOH-terminal region. Two-site immunometric assays have been developed using these new antibodies, B151 and B152. The former exhibits good specificity for hCGn independent of the source of the hCGn, the form excreted by choriocarcinoma patients or the form of hCGn from normal pregnancies. The latter antibody, B152, is sensitive to the carbohydrate moieties and possibly other differences in hCG isoforms, but is not for nicking of the beta-subunit. These two immunometric assays provide potential novel diagnostic tools for direct measurement of hCG isoforms which could not be accurately quantified earlier before development of the assays using these newly generated antibodies.

PMID: 10451222 [PubMed - indexed for MEDLINE]

☐ 1: J Endocrinol. 1993 Dec;139(3):511-8. Related Articles, Links

Immunological activities of highly purified isoforms of human FSH correlate with in vitro bioactivities.

Burgon PG, Robertson DM, Stanton PG, Hearn MT.

Prince Henry's Institute of Medical Research, Monash Medical Centre, Clayton, Victoria, Australia.

In a recent study, a five- to eightfold range in human FSH radioreceptor activity (RRA) was documented for highly purified isoforms of FSH when the data were expressed on an FSH protein content basis as determined by amino acid analysis. This study examined the FSH in vitro bioactivity and immunoactivity of these preparations. FSH in vitro biological activity showed a five- to eightfold range in activity with a high correlation with the RRA values ($r = 0.82$). A similar five- to eightfold range of values was obtained with a specific FSH radioimmunoassay and an FSH two-site immunoassay with high correlations again observed between each other, between each immunoassay and with either the in vitro bioassay or the RRA method ($r = 0.77$-0.995). Although there was overall a close correlation between these assays, significant differences in ratios of activities between the in vitro bioassay and other methods were observed with highly purified FSH isoform preparations from different pI regions. The high correlation between in vitro bioassay/RRA methods and immunoassay methods over a wide range of isoform specific activities suggests that these methods are detecting similar structural features on each isoform. It is thus concluded that these immunoassays are not solely measuring hormone mass based entirely on amino acid composition. This conclusion raises questions about ratio measurements of FSH, where immunoassay methods are presumed to measure total protein content, and their application in physiological situations and clinical practice.

PMID: 8133217 [PubMed - indexed for MEDLINE

Cytotechnology. 1994;15(1-3):217-21. Related Articles, Links

Role of environmental conditions on the expression levels, glycoform pattern and levels of sialyltransferase for hFSH produced by recombinant CHO cells.

Chotigeat W, Watanapokasin Y, Mahler S, Gray PP.

Department of Biotechnology, University of New South Wales, Sydney, Australia.

A recombinant CHO cell line in which the expression of human follicle stimulating hormone (hFSH) was under the control of the beta actin promoter was maintained in steady state perfusion cultures on a protein free medium. The level of expression of the hFSH was controlled by varying the steady state level of dissolved oxygen (10-90% of air saturation) and of sodium butyrate (0-1.5mM). Under these conditions, the specific productivity of hFSH (qFSH) varied from 0.7 to 4.8 ng hFSH/10(6) cells/h. As the specific productivity of hFSH increased, there was a shift in the FSH isoforms to the lower pI fractions, corresponding to increased sialic acid content. As the specific productivity of hFSH increased, shifting the isoform distribution towards the lower pI isoforms, that the sialyltransferase enzymic activity also increased.

PMID: 7765934 [PubMed - indexed for MEDLINE

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Volume 51 Issue 1

Mutation screening and isoform prevalence of the follicle stimulating hormone receptor gene in women with premature ovarian failure, resistant ovary syndrome and polycystic ovary syndrome

Gerard S. Conway[1], Emily Conway[1], Caroline Walker[1], W. Hoppner[2], J. Gromoll[3] & M. Simoni[3]

OBJECTIVE

To determine whether mutations in the FSH receptor gene are associated with premature ovarian failure (POF) or resistant ovary syndrome (ROS) in women in the UK. To determine whether an allelic variant of the FSH receptor gene affects fertility parameters in women with polycystic ovary syndrome (PCOS).

DESIGN

A mutation screen using DNA from women with POF and ROS. Restriction digest of amplified DNA from women with POF, ROS, PCOS and controls to determine allelic variant status. Fertility parameters were compared between allelic variant subgroups of women with PCOS.

PATIENTS

The study population comprised 49 women with POF, 5 with ROS, 93 with PCOS and 51 controls.

MEASUREMENTS

In women with PCOS, fertility and menstrual status was recorded and serum FSH and ovarian volume were measured.

RESULTS

No mutation of the FSH receptor gene was found in women with POF or ROS. The allelic variant Thr^{307}/Ser^{680} was found to be similarly prevalent in all study groups. The Thr^{307}/Ser^{680} variant was found to have no phenotype in terms of fertility parameters in women with PCOS.

CONCLUSIONS

Mutations of the FSH receptor gene are rare in women with premature ovarian failure or resistant ovary syndrome in the UK. Polymorphisms of the FSH receptor gene do not appear to have pathophysiological significance with regard to ovarian function.

Clin Endocrinol (Oxf). 1999 Jul;51(1):97-9. Related Articles, Links

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Mutation screening and isoform prevalence of the follicle stimulating hormone receptor gene in women with premature ovarian failure, resistant ovary syndrome and polycystic ovary syndrome.

Conway GS, Conway E, Walker C, Hoppner W, Gromoll J, Simoni M.

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OBJECTIVE: To determine whether mutations in the FSH receptor gene are associated with premature ovarian failure (POF) or resistant ovary syndrome (ROS) in women in the UK. To determine whether an allelic variant of the FSH receptor gene affects fertility parameters in women with polycystic ovary syndrome (PCOS). DESIGN: A mutation screen using DNA from women with POF and ROS. Restriction digest of amplified DNA from women with POF, ROS, PCOS and controls to determine allelic variant status. Fertility parameters were compared between allelic variant subgroups of women with PCOS. PATIENTS: The study population comprised 49 women with POF, 5 with ROS, 93 with PCOS and 51 controls. MEASUREMENTS: In women with PCOS, fertility and menstrual status was recorded and serum FSH and ovarian volume were measured. RESULTS: No mutation of the FSH receptor gene was found in women with POF or ROS. The allelic variant Thr307/Ser680 was found to be similarly prevalent in all study groups. The Thr307/Ser680 variant was found to have no phenotype in terms of fertility parameters in women with PCOS. CONCLUSIONS: Mutations of the FSH receptor gene are rare in women with premature ovarian failure or resistant ovary syndrome in the UK. Polymorphisms of the FSH receptor gene do not appear to have pathophysiological significance with regard to ovarian function.

1: Hum Reprod. 1991 Mar;6(3):346-50. Related Articles, Links

Preponderance of basic isoforms of serum luteinizing hormone (LH) is associated with the high bio/immune ratio of LH in healthy women and in women with polycystic ovarian disease.

Ding YQ, Huhtaniemi I.

Department of Physiology, University of Turku, Finland.

In an attempt to correlate serum LH isoform distribution with its bio/immuno ratio, follicular phase blood samples from four normally cycling women and four patients with polycystic ovarian disease (PCOD) were studied. Chromatofocusing of peripheral serum samples across a pH gradient of 9.5-4.5 yielded a broad area of LH immunoreactivity comprising several peaks in the pH range of 7.2-9.0, and six other major peaks at pH values of 9.4, 6.8, 6.4, 5.1, 4.7 and less than 4.0. In addition, the bioactive and immunoreactive levels of LH were measured in the unfractionated serum samples. In three out of four PCOD patients and one healthy woman, the majority of LH species (approximately 70%) were distributed at a pI value greater than 7.0. All of them had a high bio/immuno ratio (greater than 2.0) and an elevated bioactive level of serum LH (greater than 40 IU/l). Conversely, fewer alkaline pI isoforms of LH were found in the other three normal women and one PCOD patient, who had low levels of the bio/immuno ratio of LH (less than 2.0) and bioactive LH (less than 40 IU/l). A significant (P less than 0.05) direct correlation was observed between the bio/immuno ratio of serum LH and the proportion of alkaline LH eluted. In conclusion, as demonstrated previously in the pituitary, the bio/immuno ratio of serum LH also correlates well with the charge distribution of LH isoforms. The results indicate that an altered isoform distribution with more basic LH forms is associated with a high biological activity of serum LH.

PMID: 1955538 [PubMed - indexed for MEDLINE]

☐ 1: J Clin Endocrinol Metab. 1994 Sep;79(3):756-60. Related Articles, Links

Increased biological activity due to basic isoforms in recombinant human follicle-stimulating hormone produced in a human cell line.

Flack MR, Bennet AP, Froehlich J, Anasti JN, Nisula BC.

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FSH has four asparagine-linked oligosaccharides with variable sialic acid contents, so that FSH is not a single molecule, but a heterogeneous group of isoforms. These isoforms differ in their biological properties and their distribution changes in various physiological states, allowing the modulation of FSH activity. Recombinant human (h) FSH has been produced in Chinese hamster ovary cells and has an isoform profile similar to those of both pituitary FSH standard and purified urinary FSH. These FSH preparations, however, do not contain the full spectrum of FSH isoforms found in the circulation. Production of recombinant hFSH in a cell line with a different pattern of glycosylation could broaden its isoform profile and potentially alter its biological activity. Thus, we transfected human embryonal kidney cells (293) with the human alpha and FSH beta genes to produce recombinant hFSH (hFSH-293) and determined its biological activity in a rat granulosa cell bioassay. Although hFSH-293 was immunologically indistinguishable from pituitary FSH standard, its biological potency was 3- to 6-fold higher than those of two different pituitary FSH standards. To investigate this increased potency, we separated the isoforms of hFSH-293 by chromatofocusing and determined their biological potencies in the rat granulosa cell bioassay. The isoform profile of hFSH-293 demonstrated a greater number of basic isoforms than that of pituitary FSH standard. Several of these basic isoforms exhibited enhanced in vitro biological potency, accounting for the increased biological potency of hFSH-293. This pattern of high in vitro biological activity and more basic isoforms is analogous to the FSH circulating during GnRH stimulation, pubertal induction, and ovulation.

PMID: 8077357 [PubMed - indexed for MEDLINE]

: J Clin Endocrinol Metab. 1995 Apr;80(4):1257-63. Related Articles, Links

Occurrence and biological properties of a common genetic variant of luteinizing hormone.

Haavisto AM, Pettersson K, Bergendahl M, Virkamaki A, Huhtaniemi I.

Department of Physiology, University of Turku, Finland.

We have characterized the frequency and selected biological properties of a variant form of LH caused by two point mutations in the gene of the LH beta-subunit. Detection of the LH variant (or polymorphism) is based on aberrant immunoreactivity; it is not detected by a monoclonal antibody (Mab) recognizing a specific epitope in the LH alpha/beta-dimer (assay 1), but an assay using two LH beta-specific Mab recognizes this LH form normally (assay 2). Hence, the ratio of LH measured by assays 1 and 2 is 1.18-2.10 (range of mean +/- 2 SD) in wild-type subjects, 0.54-0.98 in heterozygotes, and below 0.15 in homozygotes with regard to the mutant LH beta allele. Analysis of sera from 249 healthy male and female subjects of Finnish origin revealed a frequency of 24.1% heterozygotes and 3.6% homozygotes for the mutation, with similar proportions in each sex. The ratio of in vitro bioactivity to immunoreactivity (assay 2) of the variant LH was significantly ($P < 0.01$) increased (2.9 +/- 0.1; $n = 11$) compared to that of wild-type LH (2.2 +/- 0.1; $n = 13$). No difference was observed in LH pulsatility, measured from blood samples collected at 5-min intervals for 5 h, between three male and three female subjects homozygous for the LH variant and three matched male and three female controls with wild-type LH. Likewise, the responses of LH immunoreactivity (assay 2) to GnRH stimulation were similar with both types of LH. The half-time of the variant LH in rat circulation from both sexes was significantly shorter than that of LH from control subjects (males, 25.5 +/- 3.8 vs. 48.3 +/- 2.7 min, respectively; $P < 0.01$; $n = 3$). Upon isoelectric focusing of peripheral serum samples, the isoform distribution of the variant LH was similar to that of wild-type LH. In conclusion, the LH variant discovered by us appears to occur with high frequency in the Finnish population (28% homo- or heterozygotes). It has increased in vitro bioactivity and a decreased half-time in vivo. These differences are compatible with a putative extra carbohydrate chain in the LH beta-chain, as one of the two mutations introduces an extra glycosylation signal. The subjects homozygous for the LH polymorphism are apparently healthy. However, the altered bioactivity and in vivo kinetics of the LH variant may induce subtle changes in LH action, either predisposing the affected individuals to or protecting them from disease conditions related to LH action.

PMID: 7714098 [PubMed - indexed for MEDLINE]

☐ 1: Ginecol Obstet Mex. 1996 Mar;64:140-5. Related Articles, Links

[Variations in the molecular forms of LH and FSH during the normal ovarian cycle]

[Article in Spanish]

Hernandez-Valencia M, **Mason M**, **Eugenia Fonseca M**, **Zarate A**.

Unidad de Investigacion Medica en Enfermedades Endocrinas, Hospital de Especialidades, Mexico.

FSH and LH concentrations during the menstrual cycle are well known, showing characteristically a midcycle surge in LH as well as in less degree in FSH. At the present there is an increasing interest in studying variations of the moleculoar forms of both gonadotropins. We have studied the chromatographic profile of FSH and LH in sera obtained from women regularly ovulating and in patients with anovulatory cycles by the use of gel column chromatography. It was observed the predominance of LH 32-34 kDa at midcycle and the heterogeneous FSH profile during the ovarian cycle. In sera from anovulatory patients the chromatographic profile was even more irregular for both LH and FSH. It is concluded that LH 32-34 kDa may be the more biological isoform in turn related with the process of ovulation.

PMID: 8729192 [PubMed - indexed for MEDLINE]

Acta Neurobiol Exp (Wars). 1996;56(3):743-51. Related Articles, Links

Polymorphism of gonadotropin action; molecular mechanisms and clinical implications.

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Various structural alterations of gonadotropins and their receptors (R) contribute to the polymorphism of gonadotropin action. One reason is the microheterogeneity of gonadotropins due to variations in the degree of their glycosylation. This alters the intrinsic bioactivity of gonadotropins, as reflected by changes in their bioactivity to immunoreactivity ratios in various physiological and clinical conditions. We have reassesses this phenomenon by improved in vitro bioassay and immunoassay methods, and it appears that the intrinsic bioactivity of gonadotropins, in particular of LH, is more constant than previously demonstrated. The second part of this chapter deals with a common polymorphism that was recently discovered in the gene of the LH beta-subunit. The variant LH beta allele contains two point mutations, both altering the amino acid sequence (Trp8Arg and Ile 15Thr), the latter one in addition introduces a new glycosylation signal to the LH beta peptide. The variant seems to represent an evolutionary early form of LH, being structurally closer to hCG than wild-type LH. The LH variant is common world-wide, with the carrier frequency varying from 28% in Finland to 7.5% in North American Hispanics. The LH variant differs functionally from wild-type LH, and it seems to predispose the carriers to mild aberrations of reproductive function. The third section summarizes our findings on the first mutation of the FSHR gene. This inactivating missense mutation is located in the gene sequence encoding the extracellular domain of the FSHR (Ala 189Val). The mutated receptor protein is apparently incorrectly folded and devoid of biological activity. The mutation explains about 50% of the hereditary form of hypergonadotropic ovarian dysgenesis in the Finnish population.

Publication Types:
- Review

☐ 1: Acta Paediatr. 1995 Jun;84(6):655-9. Related Articles, Links

Gonadal function and glycoprotein hormones in the carbohydrate-deficient glycoprotein (CDG) syndrome.

Kristiansson B, Stibler H, Wide L.

Department of Paediatrics, University of Goteborg, Sweden.

Six females and six males with carbohydrate-deficient glycoprotein (CDG) syndrome type I, aged 4 months to 43 years, were examined for gonadal function and electrophoretic isoform patterns of four glycoprotein hormones: FSH, LH, TSH and erythropoietin. The female patients had a hypergonadotrophic hypogonadism from an early age without detectable ovaries in three cases. In the males, testosterone levels tended to be low with normal or slightly raised gonadotrophin values. None of the four glycoprotein hormone showed any signs of carbohydrate deficiency of the same type as in many liver-synthesized circulating glycoproteins. It is concluded that females with CDG syndrome type I have primary ovarian failure, and that the syndrome does not affect the terminal charged carbohydrate portion in gonadotrophins, TSH or erythropoietin. The characteristic carbohydrate deficiency in some circulating glycoproteins is thus not a generalized feature in this disease.

PMID: 7670249 [PubMed - indexed for MEDLINE

☐ 1: Clin Endocrinol (Oxf). 1999 May;50(5):619-27. Related Articles, Links

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Acidic isoforms of chorionic gonadotrophin in European and Samoan women are associated with hyperemesis gravidarum and may be thyrotrophic.

Jordan V, Grebe SK, Cooke RR, Ford HC, Larsen PD, Stone PR, Salmond CE.

Department of Pathology, Wellington School of Medicine, New Zealand.

OBJECTIVE: There is conflicting evidence concerning the role of human chorionic gonadotrophin (hCG) in the aetiology of hyperemesis gravidarum (HG); particular isoforms of hCG may be the critical factor. Ethnic differences in HG prevalence and putative thyrotrophic effects of hCG may also relate to differences in hCG isoform profiles. To address these issues we examined the relationship of hCG isoforms to HG and thyroid function tests in two groups of women from ethnic backgrounds with significantly different HG prevalence rates. PATIENTS AND DESIGN: We enrolled 10 European and 10 Samoan women with HG and an equally sized non-hyperemetic, gestational stage matched control group. MEASUREMENTS: We administered a questionnaire, generated serum hCG charge-isoform profiles by chromatofocusing and measured the serum concentrations of total hCG, oestradiol (E2), thyrotrophin (TSH) and free thyroxine (FT4). RESULTS: The mean serum total hCG levels were highest in the Samoan hyperemetics (176,268 IU/l), and overall higher in hyperemetics compared with controls (159,770 IU/l vs. 86,420 IU/l, $P < 0.001$). When compared with controls, hyperemetics displayed increased hCG concentrations in the more acidic half (pH < 4) of the chromatofocusing pH range (89,843 IU/l vs. 41,146 IU/l, $P < 0.003$). Serum E2 levels did not differ between the four groups, but correlated with the hCG concentration between pH 5.2 and 4.01. Mean serum TSH levels were significantly lower in hyperemetics than in controls (0.33 mIU/l vs. 1.19 mIU/l, $P < 0.001$) and correlated with the hCG concentration between pH 4.6 and 2.8, while serum FT4 correlated with the hCG concentration below pH 4.0. CONCLUSIONS: Acidic isoforms of hCG may play a role in the aetiology of HG and gestational thyrotoxicosis. Minor ethnic differences in hCG isoform profiles were observed, but the relationship of acidic hCG isoforms to HG and serum thyroid hormone levels was largely independent of the patients' ethnicity. The mechanisms by which acidic isoforms might provoke nausea remain uncertain, but do not seem to involve E2, while the longer half-life of acidic hCG isoforms may result in increased in vivo TSH receptor cross-talk with resultant thyrotrophic effects.

PMID: 10468928 [PubMed - indexed for MEDLINE]

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Chaos: An Interdisciplinary Journal of Nonlinear Science -- October 1991 -- Volume 1, 271-278

Menopausal hot flashes: Randomness or rhythmicity

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(Received 6 August 1991; accepted 19 August 1991)

Menopausal hot flashes are episodes of flushing, increased heart rate, skin blood flow and skin temperatı sensation of heat. The thermoregulatory and cardiovascular concomitants of hot flashes are associated w levels of various hormones and neurotransmitters in the peripheral circulation. Although hot flashes affe of women, and are the primary reason that women at menopause seek medical attention, the mechanism is still not understood. Hot flashes vary in frequency and intensity both within and between individuals, a thought of as occurring randomly. Yet, some women report that their hot flashes are worse at a particulai year. Initial examination of subjects' recordings of their hot flashes showed diurnal patterns of hot flash (There also seems to be a diurnal rhythm of hot flash intensity. Continuous physiological monitoring of h facilitating the analysis of these patterns, which is revealing circadian and ultradian periodicities. The oc flashes can be modulated by external and internal factors, including ambient temperature and fever. Rhy thermoregulatory and endocrine functions also may influence hot flash patterns. Examination of the inte between the various systems of the body involved in hot flashes, and a multidisciplinary approach to the flash patterns, will aid our understanding of this complex phenomenon. Chaos: An Interdisciplinary Jour Nonlinear Science is copyrighted by The American Institute of Physics.

doi:10.1063/1.165840
PACS: 87.90.+y, 05.45.+b Additional Information

☐ 1: J Endocrinol Invest. 1983 Dec;6(6):427-33. Related Articles, Links

Age and sex related variations in biologically active and immunoreactive serum luteinizing hormone.

Marrama P, Zaidi AA, Montanini V, Celani MF, Cioni K, Carani C, Morabito F, Resentini M, Bonati B, Baraghini GF.

Relatively recent data from the literature show some discrepancies between bioactive LH (Bio-LH) and radioimmunoreactive LH (Ria-LH) in different endocrinological conditions. In 202 subjects of both sexes we have studied biologically active and immunoreactive LH and their ratio (B/I ratio) pattern through life. The results show that in male puberty the in vitro bioassay method gives a more discriminating measurement of serum LH than the radioimmunoassay. The ratio between bioactive and immunoreactive LH is well correlated with the increase of serum testosterone levels from male prepuberty to adulthood. On the contrary, there is no difference of B/I ratio between prepubertal girls and fertile women, in spite of the different gonadotropin levels. Finally LH bioactivity increases less markedly in elderly men than in postmenopausal women. These data suggest that, among several factors which may influence not only the quantity but also the quality of LH secreted, gonadotropin secretion rate and sex steroid milieu play an important role and may partly explain the B/I ratio changes in the situations investigated.

PMID: 6672069 [PubMed - indexed for MEDLINE]

Clin Endocrinol (Oxf). 1994 Jun;40(6):743-50. Related Articles, Links

Effects of oestrogen treatment on serum gonadotrophin bioactivity, immunoreactivity and isohormone distribution, and on immunoreactive inhibin levels, in prostatic cancer patients.

Matikainen T, Haavisto AM, Permi J, de Kretser D, Huhtaniemi I.

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OBJECTIVE AND DESIGN: No data are available on effects of long-term exposure to oestrogen on bioactivity of gonadotrophins in men. We studied the effects of a 6-month oestrogen therapy on serum FSH and LH bioactivity (B), immunoreactivity (I) and isohormone distribution, and on serum I-inhibin levels, in patients with prostatic carcinoma. PATIENTS: Eleven men with advanced prostatic cancer were studied, each receiving 160 mg of polyoestradiol phosphate (Estradurin) once a month intramuscularly for 6 months. MEASUREMENTS: Serum samples were collected before, and after 2 and 6 months of oestrogen treatment. Serum B- and I-FSH levels were measured by immature rat granulosa cell bioassay and immunofluorometric (IFMA, Delfia) assay, respectively, and those of B- and I-LH by mouse interstitial cell bioassay and IFMA, respectively. Serum oestradiol (E2) concentrations were measured by IFMA assay, and serum testosterone (T) and inhibin levels by radioimmunoassay. Isoelectric focusing was used for fractionation of the FSH and LH isoforms. RESULTS: The pretreatment levels of B-FSH and I-FSH were 84.7 +/- 21.6 and 11.4 +/- 3.2 IU/l (mean +/- SEM), respectively, and the B/I ratio of FSH was 8.3 +/- 1.0. The pretreatment levels of B-LH and I-LH were 23.5 +/- 3.2 and 10.1 +/- 2.3 IU/l, respectively, and the B/I ratio was 3.0 +/- 0.4. After 6 months of oestrogen therapy, B-FSH and I-FSH decreased to 37.5 +/- 8.1 ($P < 0.05$) and 1.3 +/- 0.3 IU/l ($P < 0.01$), respectively, but the B/I ratio of FSH increased to 28.5 +/- 4.2 ($P < 0.05$). B- and I-LH levels decreased in 6 months to 7.4 +/- 0.9 and 2.3 +/- 0.5 IU/l ($P < 0.01$), respectively, but no change was found in the B/I ratio of LH. Serum T levels decreased from 19.0 +/- 2.6 to 2.7 +/- 0.9 nmol/l ($P < 0.01$) during the 6-month treatment, and the respective E2 levels increased from 0.2 +/- 0.01 to 4.4 +/- 0.5 nmol/l ($P < 0.01$). Serum I-inhibin levels were analysed from eight patients. The levels at 0, 2 and 6 months were 0.81 +/- 0.09, 0.50 +/- 0.03 and 0.54 +/- 0.01 microgram/l, respectively. Gonadotrophins in the pretreatment and 6-month samples of four patients were analysed by isoelectric focusing. In FSH of all subjects, and in LH of three subjects, a shift from acidic to more basic isoforms occurred after oestrogen therapy. This is in keeping with the increase of the B/I ratio of FSH. With LH, the isoform shift occurred between fractions with similar B/I ratios, and hence there was no shift in the overall B/I ratio. CONCLUSIONS: Oestrogen therapy of men suppressed bioactive and immunoreactive levels of gonadotrophins. The B/I ratio of FSH increased, and this increase was associated with a shift in the isohormone profile to more basic forms. In contrast, no change occurred in the B/I ratio of LH, even though changes in the isohormone profile were observed. Hence, not all changes in the isohormone distribution of gonadotrophins result in changes of the intrinsic in-vitro bioactivity.

Mol Hum Reprod. 1996 May;2(5):371-82. Related Articles, Links

Molecular biology and biochemistry of human recombinant follicle stimulating hormone (Puregon).

Olijve W, de Boer W, Mulders JW, van Wezenbeek PM.

NV Organon, Oss, The Netherlands.

Follicle stimulating hormone (FSH) is a heterodimeric glycoprotein hormone produced in the anterior pituitary gland. The hormone is essential in the regulation of reproductive processes, such as follicular development and ovulation. It is clinically used for treatment of anovulation and in assisted reproduction technologies such as in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Until recently, the only source for human FSH has been the urine from post-menopausal women. Such a natural source implies limited availability and potential product variability. Thus, we have cloned the genes encoding the alpha- and beta-subunits of human FSH and transfected these into Chinese hamster ovary (CHO) cells. A CHO-clone was isolated capable of secreting intact glycosylated FSH with identical amino acid sequences to natural FSH. This cell line was grown in perfusion culture and enabled us to isolate highly pure FSH (> 99%). The complexity of the charge distribution of human recombinant FSH was demonstrated by Isoelectric focusing. The observed microheterogeneity is caused by the large number of carbohydrate chain structures which are added to the four potential glycosylation sites in the alpha beta-dimer. Furthermore, the carbohydrates show a variation in their degree of sialylation which reflects the different pl values of the individual isohormones. Despite the complexity of post-translational modification, the isoform distribution of recombinant FSH produced in a CHO-cell line and grown in perfusion culture is surprisingly similar to that observed with pituitary FSH and urinary FSH. In conclusion, we have shown that FSH-gene transfected CHO-cells are capable of stable serum-free production of recombinant FSH. A process has been developed which assures the consistent and reproducible production of highly-purified recombinant FSH.

Publication Types:
- Review

☐ 1: J Clin Endocrinol Metab. 1988 Sep;67(3):465-73. Related Articles, Links

Modulation of serum follicle-stimulating hormone bioactivity and isoform distribution by estrogenic steroids in normal women and in gonadal dysgenesis.

Padmanabhan V, Lang LL, Sonstein J, Kelch RP, Beitins IZ.

Department of Pediatrics, University of Michigan, Ann Arbor 48109.

To determine the influence of estrogenic steroids on serum FSH bioactivity (B) and immunoreactivity (I) and the FSH isoform distribution profiles, we studied normal women during ovulatory menstrual cycles and a patient with gonadal dysgenesis treated with diethylstilbestrol (DES). Four women with ovulatory menstrual cycles, as judged from their serum immunoreactive LH, FSH, progesterone, and estradiol profiles in daily blood samples, had a significant increase in the mean FSH B/I ratio (P less than 0.05) during the midcycle phase of their menstrual cycles. Similarly, in the patient with gonadal dysgenesis the FSH B/I ratio rose significantly (P less than 0.05) after 3 weeks of DES treatment and declined during the posttreatment period. In five additional normal women, serum obtained during the follicular, midcycle, and luteal phases of their menstrual cycles was chromatofocused, and the FSH isoform distribution pattern determined. Sera obtained from the patient with gonadal dysgenesis before, during, and after DES administration were pooled and studied similarly. Chromatofocusing of a human pituitary tumor extract allowed for determination of the FSH B/I ratio in different pH ranges. The highest FSH B/I ratio was found in the more basic fractions (pH range 5.6-6.0) compared to the acidic fractions. During both the midcycle phase of the normal cycles and the DES administration period in the studies of the patient with gonadal dysgenesis, there was a shift of the FSH isoforms (as measured by immunoassay) to the basic pH range. In contrast, the mid- to late luteal phase samples, which had low B/I ratios, had an increase in FSH isoforms in the acidic pH range (less than 4.8). Similarly, in the patient with gonadal dysgenesis FSH isoforms in the basic range were more abundant during the DES treatment period than in the pre- or posttreatment serum pools. Therefore, it appears that endogenous and exogenous estrogenic stimulation alters FSH isoform distribution such that FSH isoforms that are more basic and have increased biological activity are secreted.

PMID: 3137241 [PubMed - indexed for MEDLINE]

1: J Clin Endocrinol Metab. 1992 Jan;74(1):164-71.

An immunologically anomalous luteinizing hormone variant in a healthy woman.

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An investigation was undertaken to characterize an immunological LH variant in a 31-yr-old healthy woman whose serum LH was either poorly or not at all recognized by two monoclonal antibodies. The two antibodies recognize epitopes present on the intact LH dimer, but not on the free subunits. It was found that the immunologically aberrant LH of the subject was bioactive, as evidenced by an in vitro bioassay for LH. Nothing in the personal history of the subject or in the results from a number of hormone analyses revealed any endocrine abnormalities. In a GnRH stimulation test, the increase in immunoreactive LH using two reference immunometric assays for LH was less than 10% of the mean response of five control subjects. In relative terms, the maximal increase in LH in the subject was only 60-100%, in contrast to 340-560% for the control subjects. The bio/immuno ratio of the LH in the subject was high and was further increased in the GnRH stimulation test. A low proportion of acid LH isoforms in basal and stimulated samples from the subject was in agreement with the high bio/immuno ratio. Gel filtration studies showed the presence of molecular species of apparently lower molecular size than the intact LH, but different from the free beta-subunit. The results suggest the presence of fragments of the alpha-beta-dimer where at least part of the beta-subunit has been lost. A pedigree analysis involving the parents, siblings, and children of the subject strongly suggests a genetic origin of the LH variant described with an autosomal mode of inheritance. This report on an immunological variant of LH illustrates the potential dangers of using monoclonal based immunoassays where a protein hormone with fully maintained biopotency may be partially or totally missed due to the monospecificity of the immunoreagent. This possibility should be kept in mind when inappropriately low levels of gonadotropins are detected in diagnostic routine.

☐ 1: J Androl. 1992 Jan-Feb;13(1):1-10. Related Articles, Links

Is an immunoassay available for the measurement of bioactive LH in serum?

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An in vitro bioassay for luteinizing hormone (LH) is in our opinion the "gold standard" bioassay. The rodent interstitial cell testosterone assay (RICT) is specific for bioactive LH and very sensitive, accurate, and reproducible. Diverse LH standards consistently display parallel dose-response characteristics. Sera also manifest parallel dose-response characteristics throughout reproductive life, with the exception of basal samples from prepubertal children. This indicates that all known hormones with LH bioactivity have a similar bioactive site. The in vivo bioassays for LH used for calibration of World Health Organization standards are more cumbersome and less precise and accurate than the in vitro bioassay. The ovarian ascorbic acid depletion assay corresponds better than the seminal vesicle weight assay with in vitro bioassay. Variation in the ratio of bioactive to immunoreactive LH (B/I) principally reflects variation in LH immunoassay dose-response characteristics, rather than a change in the bioactive moiety of LH. The varying B/I ratio is due to molecular heterogeneity at multiple levels. Different LH standards contain different proportions of nonbioactive but immunoreactive material. The immunoreactive LH isoforms in serum contain different proportions of bioactive material and the isoform distribution differs with reproductive status. Furthermore, the antibodies comprising the various immunoassay systems detect heterogeneous epitopes on LH, which are not necessarily bioactive. B/I ratio disparities indicate lack of specificity of immunoassays for bioactive LH. Polyclonal antibody-based radioimmunoassay requires the use of purified reagents, including a bioactive tracer, in order to achieve high specificity for bioactive LH. The new generation of monoclonal antibody-based immunometric assays yields results that are lower than, but correlate with, LH measured by the in vitro bioassay. The purest of standards, even a recombinant standard, yields results that differ up to 50% or more from one immunoassay to another. Serum LH levels also differ up to two-fold among assays. The immunometric assays have the advantage of being more sensitive and more specific for low levels of LH in serum than radioimmunoassays, but B/I ratio discrepancies remain great. An immunoassay specific for the bioactive "docking site" of human LH isoforms is still needed.

PMID: 1551801 [PubMed - indexed for MEDLINE]

Eur J Endocrinol. 1996 Oct;135(4):433-9. Related Articles, Links

Effects of gonadotropin-releasing hormone on bioactivity of follicle-stimulating hormone (FSH) and microstructure of FSH, luteinizing hormone and sex hormone-binding globulin in a testosterone-based contraceptive trial: evaluation of responders and non-responders.

Simoni M, Peters J, Behre HM, Kliesch S, Leifke E, Nieschlag E.

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Only a proportion of normal men participating in testosterone-based contraceptive trials develop azoospermia (responders). This study analyzed whether serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and sex hormone-binding globulin (SHBG) are qualitatively different between responders and non-responders. Determination of in vitro bioactive FSH after stimulation with gonadotropin-releasing hormone (GnRH) and analysis of molecular heterogeneity of serum FSH, LH and SHBG was carried out by chromatofocusing and concanavalin-A affinity chromatography in eight men who had participated in a previous contraceptive study with testosterone buciclate. Blood was withdrawn at 15-min intervals on two basal occasions and 30, 45 and 60 min after i.v. administration of GnRH (100 micrograms). Pools of sera were separated by chromatofocusing in the pH range 3-6 and by lectin chromatography on concanavalin A. Immunoreactive FSH, LH and SHBG were assayed in the eluates. Bioactive FSH was analyzed by the rat Sertoli cell bioassay. Serum bioactive FSH increased after GnRH stimulation, without significant differences between responders and non-responders. The chromatofocusing profiles of serum FSH showed a significant shift towards the less acidic region after GnRH. The isoform distribution was similar in responders and non-responders. No significant differences were found in the relative proportion of FSH, LH and SHBG retained by concanavalin A. It is concluded that the extent of suppression of sperm production by androgen administration cannot be foreseen either on the basis of the response of bioactive FSH to GnRH administration or from the glycosylation pattern of serum FSH, LH and SHBG.

Publication Types:
- Clinical Trial

PMID: 8921825 [PubMed - indexed for MEDLINE

1: J Endocrinol. 1993 Sep;138(3):529-43. Related Articles, Links

Isolation and characterization of human LH isoforms.

Stanton PG, Pozvek G, Burgon PG, Robertson DM, Hearn MT.

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Thirty-nine human LH (hLH) isoforms were chromatographically separated from human pituitary extracts using a mild purification procedure which consisted of preparative isoelectric focusing, high-performance ion-exchange chromatography and immobilized metal-affinity chromatography. Twenty of these hLH isoforms were characterized by LH radioreceptor assay, SDS-PAGE and amino acid analysis, and 17 were shown to be highly purified (> 90% pure). The specific activities of these hLH isoforms ranged from 1980 to 38,650 IU/mg protein in terms of the 2nd IS for human pituitary LH, based on protein content as determined by amino acid analysis. hFSH and hTSH content were < 0.5% and < 7.8% respectively. The purity was assessed by silver staining on SDS-PAGE. Under non-reducing conditions, a single band of apparent molecular mass 23.5-24.5 kDa was observed, whereas under reducing conditions the isoforms migrated as two distinct bands, 21.1-22.4 kDa and 18.0-20.5 kDa, probably corresponding to the alpha and beta subunits of hLH respectively. The remaining three less pure isoform preparations (70-90% pure) contained additional bands of 16 kDa and 26.3 kDa under non-reducing conditions. All isoforms showed a low molecular mass band(s) of 11-14 kDa which was < 7% of stained material as assessed by densitometry. Amino acid composition of the 17 hLH isoforms was similar to the published cDNA composition of hLH. Further fractionation of one hLH isoform (hLH IIc) on reversed-phase high-performance liquid chromatography yielded four peaks identified by N-terminal sequencing as two alpha and two beta hLH subunits identical to their cDNA-derived N-terminal sequences. No additional sequences indicative of internal clipping of hLH were observed. The two pairs of alpha and beta subunits probably represent two separate hLH isoforms in this preparation. It was concluded that a mild purification procedure with high recoveries for the isolation of intact hLH isoforms has been developed, and 17 isoforms of high purity suitable for further

☐ 1: J Endocrinol. 1993 Aug;138(2):345-9. Related Articles, Links

The Second International Standard for Human Pituitary LH: its collaborative study by bioassays and immunoassays.

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The second International Standard for Human Pituitary LH (in ampoules coded 80/552; 2nd IS) and LH 81/535 (prepared in the same way as the 2nd IS from the same LH preparation) were compared with the International Reference Preparation of Human Pituitary LH for Immunoassay (IRP 68/40) by 19 laboratories in 11 countries, using in-vivo and in-vitro bioassays, a receptor assay and immunoassays. Geometric mean estimates of the LH content of the 2nd IS (with 95% fiducial limits) in terms of IRP 68/40 were: 34.6 (29.1-41.0) IU/ampoule by in-vivo bioassays; 35.8 (27.0-47.4) IU/ampoule by in-vitro bioassays; 58.6 IU/ampoule by one receptor assay; and 36.8 (35.5-38.1) IU/ampoule by immunoassays. The close agreement between the relative activities of the 2nd IS and IRP 68/40 in the wide range of assay systems studied appears to reflect the fact that both standards contain highly purified LH with similar isoform compositions as judged by isoelectric focusing. Estimates of the LH content of LH 81/535 in terms of IRP 68/40 and in terms of the 2nd IS tended to be lower than those for the 2nd IS across all methods, but the differences were not statistically significant. The 2nd IS was found to be as suitable as IRP 68/40 as a standard for the in-vitro bioassay and immunoassay of LH in the two serum samples studied. However, the mean estimates of serum LH in terms of either of these standards were more than 150% larger by in-vitro bioassays than by immunoassays and more than 50% larger by one-site than by two-site immunoassays.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 8228742 [PubMed - indexed for MEDLINE]

☐ 1: Arch Med Res. 1995;26 Spec No:S219-30. Related Articles, Links

On the nature of the follicle-stimulating signal delivered to the ovary during exogenously controlled follicular maturation. A search into the immunological and biological attributes and the molecular composition of two preparations of urofollitropin.

Ulloa-Aguirre A, Zambrano E, Timossi C, Olivares A, Quintanar A, Aguinaga M, Diaz-Cueto L, Mendez JP.

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In the present study, we analyzed the immunological and biological potencies as well as the molecular composition of urinary follicle-stimulating hormone (FSH) present in determined lots of regular and highly purified (HP) commercial preparations of urofollitropin in order to obtain additional insights on the particular type of gonadotropin signal received by the ovary during exogenously regulated ovarian stimulation. In both preparations, a high degree of FSH charge heterogeneity was detected as disclosed by chromatofocusing analysis (pH range 7.5 to < 4.0). Urinary FSH present in the HP compound was consistently more acidic and exhibited a longer survival in rat circulation than the regular formulation. Inter-batch variability for FSH heterogeneity and in vitro bioactivity was higher in the partially purified preparation than in the HP analog. In the regular preparation, the amount of immunoreactive and bioactive FSH per ampule was two times higher than that present in the HP preparation; the resultant in vitro B/I ratios were similar. Although both urinary FSH preparations showed detectable amounts of immunoreactive and bioactive luteinizing hormone and choriogonadotropin hormone material, the degree of activity present in the less purified formulation was considerably higher than that shown by the HP analog. When the capability of each urinary FSH preparation to induce ovarian tissue-type plasminogen activator enzyme activity in hypophysectomized rats was determined, both formulations exhibited similar potencies despite the existing differences in plasma clearance rate and charge distribution profile. The present study indicates that the isoform composition of urinary FSH in the two commercial preparations analyzed differs according to the degree of purity of the formulation. More FSH material is needed in the partially purified FSH preparation to induce biological effects similar in magnitude to those exhibited by the highly purified analog. The possible impact of these variations in the molecular composition of the FSH signal on other biological functions of the ovary during the course of exogenously controlled follicular growth and maturation still remains to be ascertained.

PMID: 8845653 [PubMed - indexed for MEDLINE]

☐ 1: J Endocrinol. 1990 Apr;125(1):3-14. Related Articles, Links

Gonadotrophin glycosylation and function.

Wilson CA, Leigh AJ, Chapman AJ.

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This review emphasizes the heterogeneous structure of the gonadotrophin hormones and the influence of different oligosaccharide structures on the bioactivity of these hormones. A summary has been made of the changes in biopotency of the gonadotrophins throughout the life-cycle of the human and in different endocrine states in the rat. In general it appears that the charge of the gonadotrophin conferred by the acid radicals attached to the terminal groups on the oligosaccharide structures strongly influences biopotency. Basic structures have a greater potency in in-vitro assays, but a short half-life in the circulation, while acidic isoforms are less potent, but have a longer circulatory time and are thus more active in in-vivo estimations. More basic forms are secreted over the adult reproductive years compared with the prepubertal period and old age. The glycosyl structure of the carbohydrate groups also alters in different endocrine states and is probably also important for the bioactivity and potency of the hormone. Gonadotrophin-releasing hormone (GnRH) and gonadal steroids can influence the type of isoform synthesized and released, and therefore affect the function of gonadotrophins. GnRH enhances glycosylation, sulphation and biopotency. Oestradiol potentiates the glycosylation induced by GnRH and reduces sialylation, while testosterone increases sialylation.

Publication Types:
- Review

Mol Hum Reprod. 1996 Aug;2(8):563-71. Related Articles, Links

Studies on the relative in-vitro biological potency of the naturally-occurring isoforms of intrapituitary follicle stimulating hormone.

Zambrano E, Barrios-de-Tomasi J, Cardenas M, Ulloa-Aguirre A.

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In the present study, we analysed and compared the relative in-vitro biological activity of the various intrapituitary human follicle stimulating hormone (FSH) isoforms employing two different bioassay systems. FSH was fractionated by chromatofocusing (pH range 7.10 to < 3.80) and the several isoforms isolated were quantified at multiple dose levels by three highly specific immunoassay systems: radioimmunoassay (RIA), enzyme-immunoassay (EIA) and immunoradiometric assay (IRMA), as well as by two in-vitro bioassays, one that measures the amount of oestrogen produced by rat granulosa cells in culture and the other that determines the amount of cAMP produced by a human fetal cell line (293) expressing the recombinant human FSH receptor. The relative in-vitro biological activity of each FSH isoform, expressed as the bioassay/ immunoassay (B/I) activity ratio (B/RIA, B/EIA and B/IRMA ratios) varied with its elution pH value. Regardless of the immunoassay or bioassay method employed, less acidic FSH isoforms exhibited higher B/I ratios than their more acidic counterparts [B/RIA, B/EIA and B/IRMA ratios for isoforms with elution pH values > 4.5 = 1.05 +/- 0.13, 0.99 +/- 0.10 and 1.15 +/- 0.08 (rat oestrogen bioassay), and 2.75 +/- 0.34, 2.20 +/- 0.25 and 2.96 +/- 0.35 (human cAMP production bioassay) respectively. Ratios for isoforms with pH values < 4.5 = 0.71 +/- 0.06, 0.47 +/- 0.05 and 0.63 +/- 0.06 (rat oestrogen assay), and 1.80 +/- 0.26, 1.10 +/- 0.09 and 1.44 +/- 0.13 (cAMP assay) respectively ($P < 0.05$ for isoforms with pH < 4.5 compared with those isoforms with pH > 4.5)]. Furthermore, statistically significant direct relationships between the B/RIA, B/EIA and B/IRMA ratios and elution pH value of each isoform was identified by regression analysis [rat assay: $r = 0.844$, 0.800 and 0.780 ($P < 0.01$); human assay: $r = 0.730$, 0.845 and 0.821 ($P < 0.01$), for their corresponding B/RIA, B/EIA and B/IRMA ratios respectively]. The finding of significant differences in relative in-vitro biological potency among the various intrapituitary FSH isoforms strongly suggests that the shifts towards the production and secretion of more basic or acidic FSH molecules occurring in certain specific physiological conditions (e.g. puberty and menstrual cycle), may represent an important mechanism through which the anterior pituitary regulates gonadal function.

PMID: 9239668 [PubMed - indexed for MEDLINE]

Endocrine. 1999 Apr;10(2):113-21. Related Articles, Links

Receptor binding activity and in vitro biological activity of the human FSH charge isoforms as disclosed by heterologous and homologous assay systems: implications for the structure-function relationship of the FSH variants.

Zambrano E, Zarinan T, Olivares A, Barrios-de-Tomasi J, Ulloa-Aguirre A.

Department of Reproductive Biology, Instituto Nacional de la Nutricion Salvador Zubiran, Mexico DF, Mexico.

Follicle-stimulating hormone (FSH) is produced and secreted in multiple molecular forms. These isoforms differ in their oligosaccharide structures, which determine the particular behavior of a given variant in in vitro and in vivo systems. Employing heterologous cell assay systems, this and other laboratories have shown that highly sialylated human FSH variants exhibit lower receptor binding/immunoactivity as well as in vitro bioactivity/immunoactivity relationships than their less sialylated counterparts. It is not known, however, whether this characteristic behavior of the FSH isoforms is reproduced by homologous assay systems, in which unique variants of the receptor are presumptively expressed. To gain further insights into the structure-activity relationship of the various FSH isoforms, we analyzed the capacity of nine charge isoforms obtained after high-resolution chromatofocusing (pH window, 7.10 to <3.80) of anterior pituitary glycoprotein extracts to bind and activate their cognate receptor expressed by naturally occurring heterologous cell systems (rat granulosa cells and seminiferous tubule homogenates) as well as by human embryonic kidney-derived 293 (HEK-293) cells transfected with the human FSH (FSH-R) receptor cDNA. In both (heterologous and homologous) receptor assay systems, the isoforms displaced 125I-labeled FSH from the receptor in a dose-response manner; however, whereas in the heterologous systems, the receptor binding activity varied according to the elution pH value/sialic content of the isoforms, with the less acidic variants exhibiting higher receptor binding activity ($r = 0.851$ and 0.495 [$p < 0.01$ and $p < 0.05$] for the granulosa cell and testicular homogenate receptor assay systems, respectively) than the more acidic/sialylated analogs, in the homologous assay, this relationship was practically absent ($r = 0.372$, p N.S.). The capacity of the isoforms to induce androgen aromatization by rat granulosa cells followed the same trend shown by its corresponding receptor assay system ($r = 0.864$, $p < 0.01$). Interestingly and in contrast to the results observed in the homologous receptor binding assay, the ability of the isoforms to induce cAMP production by HEK-293 cells varied according to their elution pH value, with the more sialylated isoforms exhibiting lower potency than their less acidic counterparts ($r = 0.852$, $p < 0.01$). The results yielded by the heterologous assays suggest that the different potency of the isoforms to elicit a biological effect in a naturally occurring receptor system depends primarily on the particular affinity of the receptor molecule for each isoform. The existence of a clear dissociation between receptor binding and signal transduction in the homologous system indicate that this later function is rather related to the different ability of the FSH glycosylation variants to induce and/or stabilize distinct receptor conformations that may permit preferential or different degrees of activation/inhibition of a given signal transduction pathway. Thus, the human FSH receptor-transducer system apparently possesses sufficient versatility to respond in a different manner to glycosylation-dependent diverse FSH signals.

PMID: 10451219 [PubMed - indexed for MEDLINE]

1: Br J Gen Pract. 1997 Mar;47(416):161-5. Related Articles, Links

Comment in:
- Br J Gen Pract. 1997 Jul;47(420):462-3.
- Br J Gen Pract. 1997 Oct;47(423):663.

Adequacy of hormone replacement therapy for osteoporosis prevention assessed by serum oestradiol measurement, and the degree of association with menopausal symptoms.

Rodgers M, Miller JE.

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BACKGROUND: Patients on hormone replacement therapy (HRT) for osteoporosis prevention rather than menopausal symptom control may be asymptomatic, despite inadequate replacement and low serum oestradiol (E2) levels. In the primary health care setting, therapeutic monitoring of HRT is not carried out routinely so that patients with serum E2 levels inadequate to protect bone may be missed. AIM: To determine the proportion of women on transdermal E2 preparations with serum E2 levels insufficient to protect bone and to assess the value of a questionnaire-derived menopausal symptom score (MSS) for detecting these patients. METHOD: A cross-sectional analysis of 45 patients aged 35-70 years using transdermal E2 preparations obtained from a computer register of 14500 patients in a suburban practice. One blood sample was obtained from each patient at the time the MSS questionnaire was completed. Serum E2 concentration was measured using a fluoroimmunoassay and compared with the MSS. Levels below 150 pmol/l were considered to be insufficient to protect bone. The diagnostic accuracy of the MSS in screening for levels below 150 pmol/l was determined using receiver operating characteristic (ROC) curve analysis. RESULTS: The median (95% CI) serum E2 was 147 pmol/l (126-198 pmol/l) and levels were below 150 pmol/l in 24 out of 45 patients. There was no difference in the MSS (median, 95% CI) between those with serum E2 < 150 pmol/l (8.5, 5.0-17) and > or = 150 pmol/l (9.0, 5.0-14; P = 0.477). The degree of association between the serum E2 and the MSS, using the Spearman rank correlation coefficient, rs (95% CI) was small and not significant (-0.04, -0.34 to 0.26; P = 0.398). ROC curve

analysis revealed an area under the curve (95% CI) of 0.51 (0.33-0.68). CONCLUSIONS: More than half the women were inadequately replaced to protect against osteoporosis. Furthermore, the MSS was of no value in screening for those with low serum E2 levels. Serum E2 levels should be monitored in women on HRT for osteoporosis prevention and the E2 dosage adjusted accordingly.

PMID: 9167320 [PubMed - indexed for MEDLINE]

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1: Int J Fertil Womens Med. 1997 Mar-Apr;42(2):78-84. Related Articles, Links

Hormone replacement therapy in the menopause.

Sarrel PM.

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The failure of follicular development that characterizes the menopause leads to a marked reduction in serum levels of estradiol and progesterone. As a result, the majority of women develop symptoms, including hot flushes, sleep disturbance, and vaginal dryness. Long-term consequences of ovarian insufficiency include genital atrophy, osteoporosis, and increased rates of myocardial infarction. Estradiol replacement (ERT) has proved effective in treating and preventing these problems. ERT has, however, led to increased risk of endometrial carcinoma. Consequently, treatment regimens now include progestins (HRT) to protect women who have a uterus. Progestins act by down-regulation of estradiol receptor activity, which is an advantage for preventing endometrial hyperstimulation, but a potential disadvantage when beneficial effects of estradiol are opposed. Current menopause health care includes assessment, treatment, and follow-up. Signs and symptoms of estradiol deficiency are evaluated during initial history-taking and physical examination. The MENSI (Menopause Symptom Index) has proved an efficient questionnaire for both initial assessment and monitoring of treatment effects. Vaginal cell maturation index (M.I.) can be helpful in determining need for hormonal treatment and for assessing response to treatment. A "therapeutic range" for ERT can be achieved with the availability of a variety of hormone preparations administered in different ways (oral, transdermal, skin gel, implants, etc.), thus avoiding the problems of both inadequate and excessive hormonal doses. This paper will describe a structured approach to the delivery of health care in the menopause.

Publication Types:
- Review

PMID: 9160217 [PubMed - indexed for MEDLINE]

Mol Hum Reprod. 1996 Sep;2(9):643-50. Related Articles, Links

More in-vitro bioactive, shorter-lived human chorionic gonadotrophin charge isoforms increase at the end of the first and during the third trimesters of gestation.

Diaz-Cueto L, Barrios-de-Tomasi J, Timossi C, Mendez JP, Ulloa-Aguirre A.

Department of Reproductive Biology, Instituto Nacional de la Nutricion Salvador Zubiran, Mexico D.F., Mexico.

In the present study we analysed the dynamics of serum human chorionic gonadotrophin (HCG) charge isoform distribution throughout normal gestation and characterized some of the biological features of the several HCG glycoforms present in the circulation of pregnant women. Blood samples were obtained from normal pregnant women at 10-11, 12-15, 23-26 and 35-38 weeks of gestation. The sera were fractionated by preparative chromatofocusing and the separated HCG isoforms were identified and quantified by radioimmunoassay. The in-vitro biological activity and the plasma half-life of the several circulating HCG isoforms were determined by conventional methods. HCG isoforms became less acidic as pregnancy advanced. In samples taken at 10-11 weeks of gestation, the most acidic HCG molecules (pH < 3.7) comprised > 80% of total HCG recovered after chromatofocusing; this proportion decreased to 58, 60 and 47% in samples taken from weeks 12.1 to 38.4 of gestation. Meanwhile, the relative proportion of less acidic isoforms recovered within pH values 6.49-4.50 increased at the end of the first trimester (12-15 weeks), remained constant until weeks 23-26 and then increased further by the end of the third trimester. Less acidic isoforms had higher in-vitro biological potency per immunological unit than the more acidic analogues. Regardless of the trimester of pregnancy, the plasma half-life of the highly acidic (elution pH < 3.7) isoforms varied from 84.4 to 150 min (116.3 +/- 23.0; mean +/- SD), whereas the corresponding half-life of mid-acidic (pH 4.25-5.31) and low-acidic (pH 5.74-6.50) HCG isoforms ranged from 31.0 to 115.3 (75.5 +/- 20.6) and 15.3 to 58.3 (41.2 +/- 14.3) min respectively ($P < 0.01$, highly acidic versus mid- and low-acidic analogues and mid-acidic versus least acidic isoforms). The overall data indicate that the human trophoblast is able to regulate the exact intensity, biochemical composition and duration of the gonadotrophic stimulus secreted during the course of normal gestation. They also suggest that the decrease and maintenance of low serum HCG concentrations during the second and third trimesters of gestation may be partially caused by changes in the carbohydrate structure of the HCG molecule.

PMID: 9239677 [PubMed - indexed for MEDLINE]

☐ 1: Mol Cell Endocrinol. 1996 Dec 20;125(1-2):133-41. Related Articles, Links

Structural and functional characterisation of hFSH and hLH isoforms.

Stanton PG, Burgon PG, Hearn MT, Robertson DM.

Prince Henry's Institute of Medical Research, Clayton, Victoria, Australia.

Human follicle-stimulating hormone (hFSH) and luteinizing hormone (hLH) are gonadotropins which are secreted as multiple forms by the pituitary. Evidence supporting the structural and functional heterogeneity of 15 purified hFSH isoforms and 20 purified hLH isoforms from pituitary extracts will be presented. Gonadotropin isoforms were purified by a combination of preparative isoelectric focusing and ion-exchange chromatography. The protein mass of each isoform was determined by amino acid analysis, which also correlated (data for hLH) ($r = 0.999$, $P < 0.001$, $n = 15$) with the UV area under the curve at 280 nm of the isoforms following gel-filtration HPLC. The alpha and beta subunits of FSH and LH were shown to be intact by SDS-PAGE under reducing condition, with no evidence of proteolytic nicking or presence of contaminating proteins. hFSH radioreceptor activity varied over a seven-fold range, and a positive correlation ($r = 0.85$, $P < 0.001$, $n = 9$) was observed between FSH receptor activity and the sialic acid (SA) content (1.5-13.7 mol SA/mol hFSH) of the isoforms, as determined by an HPLC-based microfluorometric assay. FSH in vitro activities varied over a similar range with a high correlation ($r = 0.82$, $n = 15$) with receptor activities, suggesting that the initial association of the hormone with the receptor is the key interaction with less differences attributed to subsequent effects in the signaling pathway. A similar result was seen with the hLH isoforms. To explore FSH/LH in vivo, the circulating half-life (LH/FSH) and the in vivo bioactivity (LH) using an acute in vivo assay was investigated. The clearance of hLH and hFSH showed a bi-exponential pattern for all isoform preparations with the proportion of the slower dissociating component (t 1/2 50-60 min) increasing three-fold with increasing sialic acid content of the isoform. The more rapidly cleared component (t 1/2 approx 10 min) is attributed to hepatically cleared gonadotropin, rather than gonadotropin equilibration between body compartments. The in vivo assay procedure for LH was based on the 24 h integrated plasma testosterone levels in rats following administration of graded doses of hLH isoform or standard. A 16-fold range in vivo activities between LH isoforms ($n = 14$) was observed. A comparison between hLH in vitro and in vivo activities showed a good correlation ($r = 0.75$) with the slope of the regression line (1.39) not significantly different from unity. These results suggest that in this acute in vivo assay method, the differences in circulating half-lives between hLH isoforms although large is not a key factor in their in vivo activity. However, in chronic in vivo assay systems the differences in clearance rates between isoforms may be important in their subsequent biological response. It is concluded that structural heterogeneity of FSH and LH contributes to functional differences, with a key interaction occurring at the receptor level. The contribution of sialic acid to these activities was also investigated.

Publication Types:
- Review

Reprod Fertil Dev. 1997;9(5):501-8. Related Articles, Links

Effect of desialylation of highly purified isoforms of human luteinizing hormone on their bioactivity in vitro, radioreceptor activity and immunoactivity.

Burgon PG, Stanton PG, Pettersson K, Robertson DM.

Prince Henry's Institute of Medical Research, Monash Medical Centre, Clayton, Vic., Australia.

To establish whether sialic acid content is responsible for an observed 7-8-fold variability in bioactivity in vitro of highly purified human pituitary luteinizing hormone (hLH) isoforms, the bioactivity in vitro, radioreceptor activity and immunoactivity of hLH isoforms were determined before and after enzymatic desialylation. Three immunofluorometric assays with different hLH specificities allowed characterization of 13-24 pituitary hLH isoform preparations of pI 7.03-8.98 in terms of sialic acid content (1-5 sialic acid residues per LH molecule), bioactivity in vitro (4030-30,000 I.U. mg[-1]), radioreceptor activity (6420-25,400 I.U. mg[-1]) and hLH immunoactivity (2900-4400 to 18,300-27,300 I.U. mg[-1]). Significant positive correlations between sialic acid content and either immunoactivity or in vitro bioactivity were observed, whereas radioreceptor activity showed a curvilinear response. Following more than 90% removal of sialic acid, both in vitro bioactivity and radioreceptor activity were increased, although specific activity still differed between isoforms; immunoactivities were unaffected. It is concluded that the presence of the sialic acid residue(s) on hLH isoforms does partially contribute to the in vitro bioactivity and radioreceptor activity of the isoforms, but that hLH immunoactivity is independent of sialic acid content.

PMID: 9418979 [PubMed - indexed for MEDLINE]

Neuroendocrinology. 1998 Mar;67(3):153-63. Related Articles, Links

Full Text

A naturally occurring basically charged human follicle-stimulating hormone (FSH) variant inhibits FSH-induced androgen aromatization and tissue-type plasminogen activator enzyme activity in vitro.

Timossi CM, Barrios de Tomasi J, Zambrano E, Gonzalez R, Ulloa-Aguirre A.

Department of Pharmacology, Faculty of Medicine, Universidad Nacional Autonoma de Mexico, Mexico, DF.

It is well known that deglycosylation of gonadotropins by enzymatic or chemical procedures or by deletion of sites for N-linked glycosylation produces antagonistic analogs which are able to interact strongly with the receptor and to inhibit binding of the wild-type hormone. In the present study, we analyzed the antagonistic properties of a naturally occurring basic follicle-stimulating hormone (FSH) charge isoform obtained after high-resolution chromatofocusing of human anterior pituitary glycoprotein extracts. Coincubation of increasing amounts of this isoform with a highly purified human pituitary FSH preparation or with recombinant human FSH at doses equivalent to their corresponding ED50 for estradiol and tissue-type plasminogen activator (tPA) production, inhibited FSH-induced estrogen production and tPA enzyme activity by cultured rat granulosa cells in a dose-dependent manner. These inhibitory effects were apparently exerted at steps following 3',5'-cyclic adenosine monophosphate (cAMP) formation and did not involve activation of the protein kinase C pathway since: (a) at low doses, this basic FSH isoform moderately increased FSH-induced cAMP production by cultured rat granulosa cells; (b) coincubation of the antagonist isoform with dibutyryl cAMP completely inhibited the effects of this cAMP analog on estrogen and tPA production; (c) the isoform was able to stimulate production of cAMP in a human fetal cell line expressing the recombinant human FSH receptor, and (d) the inhibitory effects of the isoform were not affected by staurosporine, a protein kinase C inhibitor. The effects of this isoform upon dibutyryl cAMP-induced estrogen and tPA production were blocked by the addition of a highly specific antibody directed against human FSH, further demonstrating that the antagonistic effects observed were due to FSH-like molecules. In contrast to the inhibitory effects exhibited by this basic FSH isoform, a more acidic FSH charge variant consistently acted as an agonist of pituitary and recombinant FSH on both estrogen production and induction of tPA enzyme activity. These results indicate that the anterior pituitary gland normally produces FSH isoforms which act as either agonists or antagonists of FSH at the target cell level.

Mol Cell Endocrinol. 1996 Dec 20;125(1-2):133-41. Related Articles, Links

Structural and functional characterisation of hFSH and hLH isoforms.

Stanton PG, Burgon PG, Hearn MT, Robertson DM.

Prince Henry's Institute of Medical Research, Clayton, Victoria, Australia.

Human follicle-stimulating hormone (hFSH) and luteinizing hormone (hLH) are gonadotropins which are secreted as multiple forms by the pituitary. Evidence supporting the structural and functional heterogeneity of 15 purified hFSH isoforms and 20 purified hLH isoforms from pituitary extracts will be presented. Gonadotropin isoforms were purified by a combination of preparative isoelectric focusing and ion-exchange chromatography. The protein mass of each isoform was determined by amino acid analysis, which also correlated (data for hLH) ($r = 0.999$, $P < 0.001$, $n = 15$) with the UV area under the curve at 280 nm of the isoforms following gel-filtration HPLC. The alpha and beta subunits of FSH and LH were shown to be intact by SDS-PAGE under reducing condition, with no evidence of proteolytic nicking or presence of contaminating proteins. hFSH radioreceptor activity varied over a seven-fold range, and a positive correlation ($r = 0.85$, $P < 0.001$, $n = 9$) was observed between FSH receptor activity and the sialic acid (SA) content (1.5-13.7 mol SA/mol hFSH) of the isoforms, as determined by an HPLC-based microfluorometric assay. FSH in vitro activities varied over a similar range with a high correlation ($r = 0.82$, $n = 15$) with receptor activities, suggesting that the initial association of the hormone with the receptor is the key interaction with less differences attributed to subsequent effects in the signaling pathway. A similar result was seen with the hLH isoforms. To explore FSH/LH in vivo, the circulating half-life (LH/FSH) and the in vivo bioactivity (LH) using an acute in vivo assay was investigated. The clearance of hLH and hFSH showed a bi-exponential pattern for all isoform preparations with the proportion of the slower dissociating component (t 1/2 50-60 min) increasing three-fold with increasing sialic acid content of the isoform. The more rapidly cleared component (t 1/2 approx 10 min) is attributed to hepatically cleared gonadotropin, rather than gonadotropin equilibration between body compartments. The in vivo assay procedure for LH was based on the 24 h integrated plasma testosterone levels in rats following administration of graded doses of hLH isoform or standard. A 16-fold range in vivo activities between LH isoforms ($n = 14$) was observed. A comparison between hLH in vitro and in vivo activities showed a good correlation ($r = 0.75$) with the slope of the regression line (1.39) not significantly different from unity. These results suggest that in this acute in vivo assay method, the differences in circulating half-lives between hLH isoforms although large is not a key factor in their in vivo activity. However, in chronic in vivo assay systems the differences in clearance rates between isoforms may be important in their subsequent biological response. It is concluded that structural heterogeneity of FSH and LH contributes to functional differences, with a key interaction occurring at the receptor level. The contribution of sialic acid to these activities was also investigated.

Publication Types:
- Review

J Reprod Fertil. 1997 Jul;110(2):339-45. Related Articles, Links

Circulating FSH isoform patterns during recurrent increases in FSH throughout the oestrous cycle of heifers.

Cooke DJ, Crowe MA, Roche JF.

Department of Animal Husbandry and Production, Faculty of Veterinary Medicine, University College Dublin, Ireland.

Blood samples were collected from heifers (n = 6; 450 +/- 7.7 kg) 2-4 times a day during the first and second follicular waves, and during the gonadotrophin surge to determine whether changes in circulating FSH isoforms occur during cyclic quantitative changes in FSH throughout the oestrous cycle. Serum was assayed for FSH, LH, oestradiol and progesterone. Selected samples collected during the first (samples 1-3) and second (samples 4-6) postovulatory recurrent FSH increase and during the subsequent gonadotrophin surge (samples 7 and 8) were analysed for FSH isoforms by chromatofocusing. No change ($P > 0.05$) in isoform profile occurred during the first or second recurrent FSH increase, when oestradiol concentrations were 0.6 +/- 0.07 and 0.6 +/- 0.09 pg ml-1 and progesterone concentrations were 0.03 +/- 0.01 and 2.4 +/- 0.19 ng ml-1, respectively. The percentage of FSH eluting in the pH range 7.4-7.0 increased ($P < 0.05$) from 14.2 +/- 2.2 during the luteal phase (samples 1-6) to 20.2 +/- 2.3 (sample 7) and 31.4 +/- 3.4% (sample 8) during the preovulatory gonadotrophin surge, while oestradiol concentrations were higher ($P < 0.05$; 4.9 +/- 0.39 pg ml-1) than in the luteal phase of the cycle. In summary, FSH isoform patterns did not change during the cyclic quantitative changes in FSH associated with emergence of the first or second follicular wave. However, during the gonadotrophin surge, in association with increased oestradiol concentrations, an increase in the amount of less acidic isoforms of FSH was observed. Therefore, qualitative changes in FSH are not important in the physiological regulation of follicle turnover during the luteal phase of the oestrous cycle of heifers.

PMID: 9306988 [PubMed - indexed for MEDLINE]

☐ 1: Reprod Fertil Dev. 1997;9(5):501-8. Related Articles, Links

Effect of desialylation of highly purified isoforms of human luteinizing hormone on their bioactivity in vitro, radioreceptor activity and immunoactivity.

Burgon PG, Stanton PG, Pettersson K, Robertson DM.

Prince Henry's Institute of Medical Research, Monash Medical Centre, Clayton, Vic., Australia.

To establish whether sialic acid content is responsible for an observed 7-8-fold variability in bioactivity in vitro of highly purified human pituitary luteinizing hormone (hLH) isoforms, the bioactivity in vitro, radioreceptor activity and immunoactivity of hLH isoforms were determined before and after enzymatic desialylation. Three immunofluorometric assays with different hLH specificities allowed characterization of 13-24 pituitary hLH isoform preparations of pI 7.03-8.98 in terms of sialic acid content (1-5 sialic acid residues per LH molecule), bioactivity in vitro (4030-30,000 I.U. mg[-1]), radioreceptor activity (6420-25,400 I.U. mg[-1]) and hLH immunoactivity (2900-4400 to 18,300-27,300 I.U. mg[-1]). Significant positive correlations between sialic acid content and either immunoactivity or in vitro bioactivity were observed, whereas radioreceptor activity showed a curvilinear response. Following more than 90% removal of sialic acid, both in vitro bioactivity and radioreceptor activity were increased, although specific activity still differed between isoforms; immunoactivities were unaffected. It is concluded that the presence of the sialic acid residue(s) on hLH isoforms does partially contribute to the in vitro bioactivity and radioreceptor activity of the isoforms, but that hLH immunoactivity is independent of sialic acid content.

PMID: 9418979 [PubMed - indexed for MEDLINE]

Gonadotropins

A Naturally Occurring Basically Charged Human Follicle-Stimulating Hormone (FSH) Variant Inhibits FSH-Induced Androgen Aromatization and Tissue-Type Plasminogen Activator Enzyme Activity in vitro

Carlos M. Timossi[a], Jorgelina Barrios de Tomasi[b], Elena Zambrano[b], Roberto González[c], Alfredo Ulloa-Aguirre[b,d]

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Neuroendocrinology 1998;67:153-163 (DOI: 10.1159/000054310)

: Zambrano E, Zarinan T, Olivares A, Barrios-de-Tomasi J, Ulloa-Aguirre A. Related Articles, Links

Receptor binding activity and in vitro biological activity of the human FSH charge isoforms as disclosed by heterologous and homologous assay systems: implications for the structure-function relationship of the FSH variants.

Endocrine. 1999 Apr;10(2):113-21.
PMID: 10451219 [PubMed - indexed for MEDLINE]

Birken S, Krichevsky A, O'Connor J, Schlatterer J, Cole L, Kardana A, Canfield R. Related Articles, Links

Development and characterization of antibodies to a nicked and hyperglycosylated form of hCG from a choriocarcinoma patient: generation of antibodies that differentiate between pregnancy hCG and choriocarcinoma hCG.

Endocrine. 1999 Apr;10(2):137-44.
PMID: 10451222 [PubMed - indexed for MEDLINE]

L6: Entry 9 of 16 File: EPAB Oct 10, 2001

DOCUMENT-IDENTIFIER: EP 1143249 A2
TITLE: Test methods and devices for analyte isoforms

Abstract Text (1):
CHG DATE=20011102 STATUS=O> A method and test device for differentiating between states of an analyte that can exist in different forms, such as follicle stimulating hormone (FSH). The method or test device uses a pair of specific binding agents, especially monoclonal antibodies, in two assays for the same analyte. The assays, applied to contemporaneous samples, differ from one another in format, one being a two step assay and the other being one step. A novel pair of anti-FSH monoclonal antibodies that can be used together in two such assays to differentiate pre-menopausal and post-menopausal FSH samples is disclosed.

(19) Europäisches Patentamt
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(54) Test methods and devices for analyte isoforms

(57) A method and test device for differentiating between states of an analyte that can exist in different forms, such as follicle stimulating hormone (FSH). The method or test device uses two contemporaneous assays, the first of which does not differentiate between the two analyte states and the second of which does, and the assay results are compared. A novel pair of anti-FSH monoclonal antibodies that can be used together in a sandwich-format assay to differentiate pre-menopausal and post-menopausal FSH samples is disclosed.

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(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0181167 A1**

Carney et al. (43) **Pub. Date: Sep. 16, 2004**

(54) **METHOD AND KITS FOR MONITORING WOMEN'S HEALTH**

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(21) Appl. No.: **10/797,678**

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Publication Classification

(51) **Int. Cl.**[7] **A61B 10/00**; G01N 33/53

(52) **U.S. Cl.** **600/551**; 435/7.1

(57) **ABSTRACT**

The invention provides methods and kits for monitoring the status of women's health, including HRT monitoring and determination or diagnosis of ovulation, contraception, pregnancy, menopause, polycystic ovarian disease, and female sexual dysfunction. The method comprises the steps of: (a) collecting a tear fluid from a female human; (b) determining the tear concentration of at least one hormone of relevance to female fertility, sexual differentiation or sexual dysfunction in a female human, wherein the tear concentration is diagnostics of the status of women's health.

Hum Reprod. 1992 Nov;7(10):1371-8. Related Articles, Links

Biological characterization of the isoforms of urinary human follicle-stimulating hormone contained in a purified commercial preparation.

Ulloa-Aguirre A, Damian-Matsumura P, Jimenez M, Zambrano E, Diaz-Sanchez V.

Department of Reproductive Biology, National Institute of Nutrition Salvador Zubiran, Tlalpan, Mexico D.F.

The main physicochemical and biological properties of the several isoforms of urinary follicle-stimulating hormone (uFSH) present in a commercially available uFSH preparation were analysed. Purified urinary FSH was submitted to chromatofocusing and several immunoactive forms of uFSH with isoelectric points (pI) ranging from 5.5 to 3.8 were identified. An additional isoform was detected after passing through the chromatofocusing column a 1.0 M NaCl solution (salt peak). Each uFSH isoform or pool of neighbouring isoforms (pI value 5.5-5.1, pool I, 3.8 +/- 1.0% of total immunoactivity recovered; pI value 5.0-4.6, pool II, 18.4 +/- 3.6% of total; pI value 4.5-4.3, pool III, 14.9 +/- 1.5% of total; pI value 4.1, pool IV, 8.2 +/- 1.4% of total; salt peak, pool V, 51.1 +/- 6.4% of total) eluted as single FSH peaks after Sephadex G-100 exclusion chromatography (apparent M(r) 60,000). Even though FSH present within each pool was recognized by a receptor preparation, the receptor binding activity expressed as the radioreceptor assay/radioimmunoassay (RRA/RIA) activity ratio varied with the pI value of the particular uFSH isoform tested; starting from a pI value of 5.5, the receptor binding activity of FSH decreased from 5.9 +/- 0.39 to 2.4 +/- 0.19, as the pI value of the corresponding isoform declined. A similar trend was observed when the potency of each isoform was assessed by an in-vitro bioassay. (ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 1291561 [PubMed - indexed for MEDLINE]

☐ 1: Fertil Steril. 1992 Jul;58(1):60-5. Related Articles, Links

Distribution of follicle-stimulating hormone and luteinizing hormone isoforms in sera from women with primary ovarian failure compared with that of normal reproductive and postmenopausal women.

Mason M, Fonseca E, Ruiz JE, Moran C, Zarate A.

Endocrine Research Unit, Instituto Mexicano del Seguro Social, D.F.

OBJECTIVE: To demonstrate if molecular heterogeneity of gonadotropins correlates with the type of primary gonadal failure. DESIGN AND METHODS: Aliquots of sera from women with hypogonadism were subjected to gel filtration chromatography to be assayed for follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the use of radioimmunoassay. Molecular weight (MW) of isoforms was calculated on a calibration curve obtained with molecular markers. The molecular variants were characterized on the basis of elution volume, MW, and partition coefficient. RESULTS: Chromatographic profile of sera from four women with natural menopause exhibited two FSH peaks of immunoreactivity and a heavier LH isoform. This pattern was different from that obtained in sera from women of reproductive age who presented a single peak that eluted after the corresponding standard. In six cases of idiopathic premature menopause and three more with gonadotropin-resistant ovary, the chromatographic profile showed a marked and remarkable molecular heterogeneity, particularly LH, and this was more apparent in women with resistant ovary. CONCLUSIONS: Our investigation confirms the relationship between the gonadotropin heterogeneity with the gonadal failure. The duration of the ovarian failure may influence the molecular proportion of gonadotropins and the predominance of heavier MW isohormones.

PMID: 1624024 [PubMed - indexed for MEDLINE]

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S2       2361   'GONADOTROPIN, BETA SUBUNIT, HUMAN //CHORIONIC'   (CHORION-
            IC GONADOTROPIN, BETA SUBUNIT, HUMAN)
S3         48   'GONADOTROPIN, PITUITARY, BETA-SUBUNIT II'
S4      22701   E3-E48
S5         17   E49-E50
S6       1297   E1-E12
S7     109650   R1-R15
S8      24372   E3-E27
S9      24372   E3-E20
S10     45472   R1:R11
S11    116999   S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S12     45472   S8 OR S9 OR S10
S13      3152   S11 AND S12
S14       583   S13/2000:2006
S15      2569   S13 NOT S14
S16        80   S15 AND ONSET?
S17        57   S15 AND PREDICT?
S18       136   S16 OR S17
S19        26   S18 AND PERIMENOPAUS?
S20         2   (S19 OR S18 OR S17 OR S16) AND TOTAL? AND (ISOFORM? OR GLY-
          COFORM? OR ALPHA OR BETA OR CORE)
S21     32579   S11/TI
S22        64   S21 AND S12/TI
S23        71   DETERMIN?/TI AND MENOPAUS?/TI
S24        33   'FOLLICLE STIMULATING HORMONE --DIAGNOSTIC USE'
S25       253   'FOLLICLE STIMULATING HORMONE --IMMUNOLOGY --IM'
S26         5   'FOLLICLE STIMULATING HORMONE--CHANGES'
S27         2   'FOLLICLE STIMULATING HORMONE, HUMAN --ANALYSIS'
S28         4   'FOLLICLE STIMULATING HORMONE, HUMAN --CHEMISTR'
S29         1   'FOLLICLE STIMULATING HORMONE, HUMAN --IMMUNOLO'
S30        32   'UROFOLLITROPIN'
S31      2817   R1-R5
S32      3123   S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31
S33       303   S32/2000:2006
S34      2820   S32 NOT S33
S35       682   S34 AND (IMMUNOASSAY? OR ASSAY? OR TEST?)
S36        32   S35 AND (CARBOHYDRATE? OR SUGAR? OR GLYCOSYLAT? OR GLYCOFO-
          RM? OR ISOFORM? OR VARIANT? OR MODIF?)
S37         6   S36 AND TOTAL?
S38         3   S36 AND ALPHA AND BETA
S39         0   S37 AND S38
S40         9   S37 OR S38
S41        60   PREDICT?/TI AND MENOPAUS?/TI
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First Hit

L12: Entry 9 of 63 File: PGPB Jun 16, 2005

PGPUB-DOCUMENT-NUMBER: 20050130311
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TITLE: Detection of impaired fertility

PUBLICATION-DATE: June 16, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Coley, John	Rushden Northamptonshire		GB
Miro, Fernando	Bedford		GB
Aspinall, Laurence John	Bedford		GB
Murray, Peter George	Olney Buckinghamshire		GB
Dadd, Anthony William	Sharnbrook Bedford		GB
Zhang, Zhi Gang	Putnoe		GB
Mundill, Paul	Espoo		FI

US-CL-CURRENT: 436/87; 422/61

CLAIMS:

1. A method of detecting a retarded cycle in a human female subject experiencing same, the method comprising the steps of: obtaining a sample of body fluid from the subject on each of a plurality of, but not less than three, days; testing each of the plurality of samples to determine the concentration therein of at least one analyte of significance in the ovulatory cycle; comparing a result determined from said testing with a predetermined threshold value; and, if said determined result is different from the threshold value, declaring the cycle, during which the samples were taken, to be a retarded cycle.

2. A method according to claim 1, wherein the sample of body fluid comprises a urine sample.

3. A method according to claim 1, wherein the analyte of significance comprises one or more of the following: FSH; LH; progesterone or a metabolite thereof; and estrogen or a metabolite thereof.

4. A method according to claim 1, wherein samples of body fluid are taken on consecutive days.

5. A method according to claim 1, wherein each of the plurality of samples are taken on consecutive days.

6. A method according to claim 1, wherein a plurality of samples are taken during the follicular phase.

7. A method according to claim 1, wherein the analyte comprises FSH or E3G and the

first of the plurality of samples is taken in the period day 5 to day 10, with day 1 being the first day of bleeding.

8. A method according to claim 7, wherein the first of the plurality of samples is taken in the period day 6 to day 9.

9. A method according to claim 1, wherein each of the plurality of samples is taken within the period of days 6-16, with day 1 being the first day of bleeding.

10. A method according to claim 9, wherein each of the plurality of samples is taken within the period of days 7-15.

11. A method according to claim 9, wherein each of the plurality of samples is taken within the period of days 8-14.

12. A method according to claim 1, wherein a plurality of samples are taken during the luteal phase.

13. A method according to claim 12, wherein the analyte of significance comprises LH, or is a ratio of E3G/P3G.

14. A method according to claim 1, wherein samples are taken on at least 4 days.

15. A method according to claim 14, wherein samples are taken on at least 5 days.

16. A method according to claim 14, wherein samples are taken on at least 7 days.

17. A method according to claim 1, wherein the threshold value is a population-derived threshold.

18. A method according to claim 1, wherein the threshold value is an individual threshold.

19. A method according to claim 1, wherein the analyte of significance comprises FSH and E3G and the cycle is declared to be a retarded cycle if, inter alia, said testing reveals fmean>X and fmaxday>7, wherein (i) fmean is defined as the average of FSH concentration values in mIU/ml determined from day 1 of the cycle up to, but excluding, the day on which there is a significant rise in E3G; (ii) the significant rise in E3G is defined as the day of the cycle (prior to occurrence of the LH maximum) on which the slope of the plot of E3G (against time) is maximal; (iii) X is a threshold value in the range 10-30 mIU/ml urine; (iv) and fmaxday is defined as the day of the cycle on which, allowing for urine volume variation, the FSH concentration is maximal.

20. A method according to claim 19, wherein X is in the range 10-20 mIU/ml.

21. A method according to claim 19, wherein X is in the range 12-18 mIU/ml.

22. A method according to claim 1, wherein the analyte of significance comprises FSH and E3G, and the cycle is declared to be a retarded cycle if, inter alia, said testing reveals fe ratio>Y wherein fe ratio is the sum of FSH concentration values in mIU/ml divided by the sum of E3G concentration values in ng/ml, in the period from day 1 up to, but excluding, the day of the cycle (prior to occurrence of the LH maximum) on which the slope of the plot of E3G (against time) is maximal, and wherein Y is a number in the range 37-51.

23. A method according to claim 22, wherein Y is in the range 37-41.

24. A method according to claim 22, wherein the cycle is declared to be a retarded cycle if, inter alia, said testing reveals fmean>X and fmaxday>7, wherein (i) fmean is defined as the average of FSH concentration values in mIU/ml determined from day 1 of the cycle up to, but excluding, the day on which there is a significant rise in E3G, (ii) the significant rise in E3G is defined as the day of the cycle (prior to occurrence of the LH maximum) on which the slope of the plot of E3G (against time) is maximal, (iii) X is a threshold value in the range 10-30 mIU/ml urine, (iv) and fmaxday is defined as the day of the cycle on which, allowing for urine volume variation, the FSH concentration is maximal.

25. A method according to claim 1, wherein the analyte of significance comprises urinary E3G, and the method involves the determination of a basal E3G value which is the mean urinary E3G concentration of tests conducted in the period of days 3-6 of the cycle.

26. A method according to claim 1, further comprising deeming a menopause transition to have commenced if a retarded cycle is detected.

27. A method according to claim 1, further comprising deeming impaired ovarian function as being due to a menopause transition if a retarded cycle is detected and there are no other apparent causes of impaired function in the subject.

28. A programmable electronic data processing device for use in detecting a retarded cycle in a human female subject experiencing same, the device comprising a computation circuit, responsive to at least three signals, each signal representing the concentration of an analyte of significance to the ovulatory cycle in a sample of body fluid taken on one of three different days, to: compare at least one of the signals with a predetermined threshold value; and if said signal is different from the threshold value, declare the cycle during which the samples were taken, to be a retarded cycle.

29. A device according to claim 28, further comprising: receiving means for receiving a test device used for performing an analyte concentration test; and reading means for reading, from a test device received in the receiving means, the result of an analyte concentration test performed using the test device.

30. A kit for use in detecting a retarded cycle in a human female subject experiencing same, comprising a programmable electronic data processing device according to claim 29, and a plurality of test devices.

31. A device according to claim 28, further comprising display means to indicate whether a retarded cycle has been detected.

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☐	L1	(basic and acid).clm. and (tropin or gonadotropin or hlh or hgh or hfsh or htsh or lh or fsh or gh or tsh or h-hl or h-fsh).clm.	79
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☐	L7	(method or process).clm. and l5	1132
☐	L8	(method or process).clm. same l5	953
☐	L9	L8 and l1	2
☐	L10	(tropin or gonadotropin or hlh or hgh or hfsh or htsh or lh or fsh or gh or tsh or h-hl or h-fsh).clm.	2623
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TITLE: Test methods and devices for analyte isoforms

Abstract Text (1):
CHG DATE=20011102 STATUS=O> A method and test device for differentiating between states of an analyte that can exist in different forms, such as follicle stimulating hormone (FSH). The method or test device uses two contemporaneous assays, the first of which does not differentiate between the two analyte states and the second of which does, and the assay results are compared. A novel pair of anti-FSH monoclonal antibodies that can be used together in a sandwich-format assay to differentiate pre-menopausal and post-menopausal FSH samples is disclosed.